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IN THE UNITED STATES PATENT & TRADEMARK OFFICE

IN RE APPLICATION OF	:
THOMAS BECKERT, ET AL.	: EXAMINER: SHEIKH, H.N.
SERIAL NO: 10/501,236	:
FILED: JULY 12, 2004	: GROUP ART UNIT: 1615

FOR: PHARMACEUTICAL FORMULATION FOR THE ACTIVE INGREDIENT BUDESONIDE

COMMISSIONER FOR PATENTS
ALEXANDRIA, VIRGINIA 22313

SIR:

APPEAL BRIEF

This is an appeal to the Board of Patent Appeals and Interferences (Board) under 35 U.S.C. § 134 from the August 19, 2009, Final Rejection of Claims 1-8 and 10-12 of Application 10/501,236, filed July 12, 2004. A Notice of Appeal was timely filed on December 18, 2009, with one month extension of time. This Appeal Brief is timely filed on February 18, 2010, with no extensions of time.

STATEMENT OF REAL PARTY IN INTEREST

The real party in interest in this appeal is EVONIK ROEHM Gmbh, having an address of Kirschenallee 64293, DARMSTADT, GERMANY.

STATEMENT OF RELATED APPEALS AND INTERFERENCES

Appellant/Applicant, Appellant/Applicant's legal representatives, and Appellant/Applicant's assignees, are aware of no appeals, interferences, or judicial proceedings that are related to, directly affect or would be directly affected by, or have a bearing on the decision of the Board in this appeal.

STATEMENT OF JURISDICTION

The Board has jurisdiction under 35 U.S.C. § 134. This is an appeal to the Board from the final rejection of pending Claims 1-8 and 10-12, dated August 19, 2009. A Notice of Appeal was timely filed on December 18, 2009, with one month extension of time. This Appeal Brief is timely filed on February 18, 2009, with no request for extension of time.

STATUS OF CLAIMS

Claims 1-8 and 10-12 stand twice REJECTED under 35 U.S.C. § 103.

Claims 1-8 and 10-12 are APPEALED

Claim 17 stands WITHDRAWN (non-elected invention).

Claims 9 and 13-16 are CANCELED.

The final rejection of Claims 1-8 and 10-12 under 35 U.S.C. § 103(a) over Beckert (WO 01/68058, published September 20, 2001) is APPEALED.

STATUS OF AMENDMENTS

Applicant did not file any Amendment to the claims after the August 19, 2009, final rejection. However, Applicant filed a Request For Reconsideration on October 29, 2009.

In an Advisory Action dated November 18, 2009 (AA), the Examiner indicated that the "request for reconsideration has been considered but does NOT place the application in condition for allowance" (AA, p. 1). The Examiner explained (AA., p. 2):

> Applicant's argument that "In Beckert, none of the specifically named binders is a polymer or copolymer with acidic groups" has been considered but was not persuasive. It is the position of the Examiner that Applicant has not established any unexpected or superior results attributable to the binder claimed. Note in particular that instant claim 1 is generic in terms of any specific binder, other than the recitation of the binder being a 'polymer of copolymer with acidic groups'. The prior art demonstrates a combination of the binder element with the active ingredient (budesonide). The prior art is suggestive of achieving the same objective, such as stability of the formulation, as sought by Applicant. Applicant's argument drawn to superior release rates based on the instant invention and that "Beckert shows less than 80% release of active ingredient" was not persuasive. The "less than 80% drug release" shown by Beckert, which can read on 79.999% would not be so far from the "more than 80% drug release after 30 mins" claimed by Applicant. Moreover, the determination of effective or suitable release rates is within the level of the skilled artisan, obtained via routine experimentation, to achieve optimal results.

Applicant hereby appeals the Examiner's erroneous conclusion that Claims 1-8 and 10-12 on appeal are unpatentable under 35 U.S.C. § 103 over Beckert. The Examiner's erroneous conclusion of obviousness is both inconsistent with, and contrary to, the evidence of record.

SUMMARY OF THE CLAIMED SUBJECT MATTER

Applicant's claims are directed to a multilayer pharmaceutical formulation which releases 80% of its active budesonide content after 30 minutes in a simulated intestinal environment (Spec., p. 1, ll. 6-7; p. 3, l. 22, to p. 4, l. 12). The pharmaceutical formulation comprises: (a) an inner layer comprising budesonide as the active ingredient bound in a polymeric or copolymeric binder with acidic groups, (b) an intermediate layer including a polymeric material which is soluble in the intestinal juice or extends release, and (c) an outer layer including a polymer resistant to gastric juice or an envelope resistant to gastric juice (Spec., p. 4, l. 16, to p. 5, l. 5; Claims Appendix, Claim 1).

The required active ingredient is budesonide. Budesonide is known to be effective for treating intestinal problems (Spec., p. 1, ll. 11-19). However, budesonide has low solubility in the intestinal juice (Spec., p. 2, ll. 33-35). Various attempts to improve the solubility of budesonide in the intestinal juice using water-soluble excipients have not significantly improved the low

solubility of budesonide in the intestinal juices (Spec., p. 1, ll. 21-33; p. 2, ll. 35-37).

Applicant surprisingly discovered that the combination of budesonide bound in a polymer or copolymer with acidic groups in the inner layer of a multilayer pharmaceutical formulation designed to release budesonide in the intestines successfully releases more than 80% of the budesonide content bound in the inner layer into a simulated intestinal environment after 30 minutes (Spec., p. 3, l. 22, to p. 4, l. 12; p. 4, l. 16, to p. 5, l. 5). Beckert, the only prior art over which Applicant's claims stand rejected, teaches nothing of the kind.

The rejections of separately argued Claims 3, 4, and 11 are particularly egregious because the respective claims are directed to a multilayer pharmaceutical formulation wherein: (1) the inner layer (a) comprises budesonide bound in vinylpyrrolidone/vinyl acetate copolymer (Claims Appendix, Claim 3; Spec., p. 9, ll. 27-34); (2) the intermediate layer (b) is a (meth)acrylate copolymer which comprises 40 to 100% by weight free-radical polymerized units of C_1- to C_4-alkyl esters of acrylic or methacrylic acid and up to 60% by weight (meth)acrylate monomers with an anionic group in the alkyl radical (Claims Appendix, Claim 4; Spec., p. 10, ll. 21-26); or (3) the pharmaceutical formulation is a multiparticulate form which comprises different types of pellets, where one type of pellet uniformly releases budesonide in the small intestines and the other type of pellet uniformly releases budesonide in the

large intestines (Claims Appendix, Claim 11; Spec., p. 20, ll. 6-34). Beckert does not disclose or reasonably suggest any of those featured limitations.

GROUNDS OF REJECTION TO BE REVIEWED

1. The final rejection of Claims 1, 2, 5-8, 10, and 12 under 35 U.S.C. § 103 as unpatentable in view of Beckert (WO 01/68058, published September 20, 2001). Dependent Claims 2, 5-8, 10, and 12 stand or fall together with independent Claim 1.

2. The final rejection of Claim 3 under 35 U.S.C. § 103 as unpatentable in view of Beckert is separately argued from the rejection of Claim 1.

3. The final rejection of Claim 4 under 35 U.S.C. § 103 as unpatentable in view of Beckert is separately argued from the rejection of Claim 1.

4. The final rejection of Claim 11 under 35 U.S.C. § 103 as unpatentable in view of Beckert is separately argued from the rejection of Claim 1.

ARGUMENT

Preliminary Remarks

Applicant's claimed formulation stands finally rejected as obvious to a person having ordinary skill in the art at the time the invention was made in view of Beckert's prior disclosure. However, Beckert (1) does not recognize the solubility and release problems associated with budesonide in the intestines, (2) does not disclose or reasonably suggest a pharmaceutical formulation

designed to release budesonide in the intestines which comprises an inner layer of budesonide bound in a polymer or copolymer with acidic groups, and (3) does not disclose or reasonably suggest making and using a pharmaceutical formulation designed to release budesonide in the intestines wherein the inner layer of budesonide bound in a polymer or copolymer with acidic groups releases at least 80% of its budesonide content after 30 minutes in an intestinal enviroment.

1. Rejections of Claims 1, 2, 5-8, 10, and 12 under 35 U.S.C. 103 over Beckert

Claims 1, 2, 5-8, 10, and 12 (Claims Appendix) stand finally rejected under 35 U.S.C. 103 over Beckert (WO 01/68058, published September 20, 2001). Office Action dated August 19, 1009 (OA), page 3. The Examiner has continually cited, and relied upon, Beckert '454 (U.S. Patent 6,632,454 B2, issued October 14, 2003), as an English language equivalent WO 01/68058 (OA, p. 3). We have no objection. Accordingly, hereafter we also cite, and also refer to, Beckert '454 B2.

The claimed pharmaceutical formulation comprises (Claims Appendix, Claim 1; emphasis added):

a) an inner layer including budesonide bound in a binder, "wherein the binder is a polymer or copolymer with acidic groups,"

b) an intermediate layer which is soluble in intestinal juice or extends release, and

c) an outer layer or envelope which is resistant to gastric juice.

The inner layer of the claimed formulation must release the bound budesonide in an intestinal enviroment "to the extent of more than 80% after 30 min[utes]" as represented by the release test specified in the last clause of Claim 1 designed to simulate the activity and pH in the intestines.

At page 16, lines 10-17, Applicant's Specification recognizes Beckert's disclosure and teaches (emphasis added):

> A difference from [Beckert] WO 01/68058 is according to the invention that the inner layer a) is applied to the core which comprises the active ingredient budesonide bound in a polymeric binder with acidic groups. The increased budesonide solubility which is achieved in this way results in an even more advantageous embodiment.

Applicant's Specification teaches (Spec., p. 2, ll. 33-34), "One problem with pharmaceutical formulations containing the active ingredient budesonide is the low solubility of the active ingredient." Prior art efforts to improve the solubility of budesonide have added water-soluble excipients to the formulation with some success and other resultant problems (Spec., p. 2, ll. 35-37).

Beckert '454 does not recognize any of the solubility and/or release problems associated with budesonide in the intestines. In fact, budesonide is but one of many active ingredients which Beckert '454 suggests for use as the active ingredient in its multilayer pharmaceutical products. See Beckert '452, column 3, line 35, to column 4, line 51; column 4, lines 5 and 15, naming budesonide.

Persons having ordinary skill in the art routinely seek "to improve upon what is already generally known." *In re Peterson*, 315 F.3d 1325, 1330 (Fed.

Cir. 2003)(emphasis added). Persons having ordinary skill in the art do not normally optimize or improve activity which the prior art does not reasonably suggest is in need of improvement. The inventive multilayer pharmaceutical product described in Beckert '454 is designed to "release . . . less than 5% of the active pharmaceutical ingredient during the first 2 hours of a USP release test and [release] from 30 to 80% of the active pharmaceutical ingredient 8 hours after the start of the test, wherein the pH of the test is about 1.2 during the first two hours and subsequently the pH is adjusted to about 7.0 by changing a buffer" (Beckert '454, Claim 1; emphasis added). Compared to the release of budesonide bound to a binder which is a polymer or copolymer with acid groups in Applicant's inner layer in accordance with release test USP XXIII with apparatus 2 (paddle) with 100 revolutions/min in phosphate buffer of pH 7.5 to the extent of more than 80% after 30 minutes, Figure 1 of Beckert '454 shows an active ingredient release from uncoated pellets with 5-aminosalicylic acid as the active ingredient and Kollidon 25 as the binder in accordance with release test USP XXIV with paddle method with 100 revolutions per minute in a buffer of pH 7.0 to an extent of less than 80% after 1 hour and 40% or less after 30 minutes (Beckert '454, col. 11, ll. 20-48; col. 7, ll. 19-64). The Board will also note that Beckert '454 makes no distinction between 5-aminosalicylic acid and budesonide as the active ingredient "to be released as constantly as possible in the intestine, in particular shortly before or only in the colonic region. Thus, the active pharmaceutical ingredient may be . . . in particular 5-aminosalicylic acid .

. . or budesonide" (Beckert '454, col. 3, l. 66, to col. 4, l. 5; emphasis added). Furthermore, the evidence of record establishes that the Kollidon 25 binder employed in the uncoated 5-aminosalicylic acid containing pellets Beckert '454 subjected to release test USP XXIV is a polyvinylpyrrolidone (PVP) which does not contain acidic groups. See the attached BASF Technical Information brochure dated January 2004, entitled "Soluble Kollidon® grades" (Evidence Appendix, Other Evidence).

Moreover, Beckert '454 not only does not suggest making and using a pharmaceutical formulation which releases the budesonide content in an inner layer or core to the extent of more than 80% after 30 minutes in the intestines but also would not have enabled persons having ordinary skill in the art to make and use Applicant's claimed pharmaceutical formulation with any reasonable expectation of successfully releasing the budesonide content in the inner layer or core to the extent of more than 80% after 30 minutes in the intestines. A composition of matter cannot be obvious under 35 U.S.C. 103 unless the prior art would have placed the composition in the possession of the public. To that end, the prior art must both suggest the claimed composition and enable one skilled in the art to make and use the claimed composition. *In re Hoeksema*, 399 F.2d 269, 274 (CCPA 1968). For obviousness under 35 U.S.C. 103, the prior art must not only suggest the claimed composition but also enable production of the claimed composition with reasonable expectation or likelihood of success. *Merck & Co., Inc. v. Biocraft Laboratories, Inc.*, 874

F.2d 804, 807-808 (Fed. Cir. 1989); *In re O'Farrell*, 853 F.2d 894, 903-904 (Fed. Cir. 1988); *In re Dow Chemical*, 837 F.2d 469, 473 (Fed. Cir. 1988). Beckert '454 would not have enabled persons having ordinary skill in the art to make and use Applicant's claimed pharmaceutical formulation for release of budesonide. Moreover, Beckert '454 reasonably would not have led persons having ordinary skill in the art to want to do so. The inventive multilayer pharmaceutical product described in Beckert '454 is designed to "release . . . from 30 to 80% of the active pharmaceutical ingredient 8 hours after the start of the test" (Beckert '454, Claim 1).

The Examiner appears to have rejected Applicant's claims over Beckert (WO 01/68058) because (a) Beckert '454 describes a pharmaceutical formulation comprising an active agent core which may be budesonide and may be bound to a binder such as Kollidon® 25 therein; (b) Beckert '454 describes a pharmaceutical formulation wherein one of the intermediate layer components is a copolymer Applicant claims, i.e., a copolymer of (meth)acrylic acid and (meth)acrylic acid ester including a quaternary ammonium group); and (c) Beckert '454 describes a pharmaceutical formulation comprising an outer envelope Applicant claims, i.e., a copolymer of (meth)acrylic acid and (meth)acrylic acid ester including an anionic group)(OA, pp. 3-4, bridging ¶). Applicant's Specification recognized and acknowledged Beckert's teaching as filed (Spec., p. 2, ll. 8-29; p. 16, ll. 10-17). Applicant's Specification acknowledged that there are solubility problems associated with using

budesonide as the active ingredient in multi-layer formulations (Spec., p. 2, ll. 33-37; p. 16, ll. 10-17).

Nevertheless, considering the Beckert '454 disclosure in its entirety, the Examiner found (OA, p. 4):

> The active substance can be budesonide. The dosage form includes a binder such as collidon 25 as well as an internal coat of Eudragit RS and RL [corresponding to Applicant's claimed intermediate layer] and an external enteric coating of Eudragit FS (Example 1 - pages 16-18)[corresponding to Applicant's claimed outer envelope].

Based on that evidence, the Examiner concludes, "The instant invention would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, given the teachings of Beckert." However, the Examiner's findings do not provide a sufficient factual basis for the Examiner's conclusion. As stated, Beckert's Kollidon® 25 binder is not a polymer or copolymer with acidic groups. Beckert does not recognize that budesonide has unique solubility problems. Beckert is not interested in releasing 5-aminosalicylic acid, budesonide, or any other ingredient active in the intestines to the extent of more than 80% after 30 minutes in an intestinal environment.

Beckert '454 teaches that the core of its multilayer pharmaceutical product may contain 1-95% active ingredient and further pharmaceutical excipients (Beckert '454, col. 3, ll. 11-13 and 20-21). The core may further contain (Beckert '454, col. 3, ll. 20-25):

> . . . binders such as lactose, cellulose and derivatives thereof, polyvinylpyrrolidone (PVP), humectants, disintegration promoters,

> lubricants, disintegrants, starch and derivatives thereof, sugar solubilizers or others.

None of the binders mentioned in Beckert '454 is a "polymer or copolymer with acidic groups" as all of Applicant's current claims require (Claims Appendix, Claim 1).

Beckert's examples all employ active-ingredient-containing cores produced by a powder layering process (Beckert '454, col. 7, ll. 44-45). The cores were sprayed with a binder in a fluidized bed apparatus (Beckert '454, col. 7, ll. 65-67). Beckert's examples used "Kollidon® 25" as the binder (Beckert '454, col. 7, ll. 59-61). Kollidon® 25 is not a polymer or copolymer with acidic groups.

The Examiner appears to agree with Applicant that Kollidon® 25 is a polyvinylpyrrolidone (PVP)(OA, p. 6). The Examiner also appears to agree with Applicant that Kollidon® 25 is not a polymer with acidic groups (OA, p. 6). Thus, the Examiner appears to agree with Applicant that no core binder described in Beckert '454 is a "polymer or copolymer with acidic groups" which all of Applicant's appealed claims require. Moreover, Beckert '454 does not reasonably suggest that the binder for its active ingredient should or may be a "polymer or copolymer with acidic groups". While the BASF Technical Information brochure dated January 2004, entitled "Soluble Kollidon® grades" (of record)(Evidence Appendix, Other Evidence), indicates that Kollidon® 25 is a polyvinylpyrrolidone (PVP), Applicant's Specification teaches that Kollidon®

VA64 which Applicant recommends for use as an effective binder for budesonide in the inner layer (Spec., p. 9, ll. 29-34) is a polyvinylpyrrolidone/ vinyl acetate copolymer with acidic groups. Separately argued dependent Claim 3 is specifically directed to the polyvinylpyrrolidone/vinyl acetate copolymer binder (Claims Appendix, Claim 3). The Kollidon® 25 binder described in Beckert '454 in fact is not a "polymer or copolymer with acidic groups" and the Examiner does not argue that Kollidon® 25 is a binder which is capable of releasing bound budesonide "to the extent of more than 80% after 30 min." in accordance with the release test specified in Applicant's appealed Claim 1.

Nevertheless, the Examiner argues (OA, p. 6; emphasis added):

> However, the teachings of the prior art are not limited to the examples disclosed therein. The reference as a whole must be taken into consideration. In this instance, the prior art is well aware of combining a binder component with the active agent (budesonide) and is well aware of providing a structured formulation as is presently claimed herein.

In the Advisory Action dated November 18, 2009, the Examiner finally states (AA, p. 2; emphasis added);

> Applicant's argument that "In Beckert, none of the specifically named binders is a polymer or copolymer with acidic groups" has been considered but was not persuasive. It is the position of the Examiner that Applicant has not established any unexpected or superior results attributable to the binder claimed. Note in particular that instant claim 1 is generic in terms of any specific binder, other than the recitation of the binder being a 'polymer of copolymer with acidic groups'. The prior art demonstrates a combination of the binder element with the active ingredient (budesonide). The prior art is suggestive of achieving the same objective, such as stability of the formulation, as sought by Applicant. Applicant's argument drawn to superior release rates based on the instant invention and that "Beckert shows less than 80% release of active ingredient" was not persuasive. The "less than 80% drug release"

> shown by Beckert, which can read on 79.999% would not be so far from the "more than 80% drug release after 30 mins" claimed by Applicant. Moreover, the determination of effective or suitable release rates is within the level of the skilled artisan, obtained via routine experimentation, to achieve optimal results.

With all due respect, (1) there is no teaching or reasonable suggestion in Becker '454 to employ any "polymer or copolymer with acidic groups" as the binder for budesonide or any other active agent in its core; (2) Becker does not prima facie suggest using a binder with acidic groups for budesonide in the core; (3) absent a prima facie case of obviousness, Applicant is not required to show unexpected results to establish the patentability of the invention Applicant claims; (4) Beckert '454 teaches an active ingredient release to the extent less than 80% drug release after 8 hours in an intestinal environment, not an active ingredient release to the extent more than 80% drug release after 30 minutes in an intestinal environment (Beckert '454, Claim 1); and (5) Bechert '454 does not seek or intend to increase the rate of release of active ingredient released by its multilayer pharmaceutical product in the intestines or shorten the time in which more than 80% of the active agent is released in the intestines to 30 minutes.

Finally, the Examiner erred in concluding that Applicant's claims do not recite, and Applicant has not shown, unexpectedly improved budesonide solubility or release in an intestinal environment, i.e., that the solubility and release problems associated with budesonide are solved by binding budesonide to a polymer or copolymer with acidic groups. The appealed claims and

evidence of record show otherwise. Claim 1 requires that "the formulation of the inner layer without intermediate and outer layer releases the bound active ingredient in the release test according to USP XXIII monograph <711> "Dissolution" with apparatus 2 (paddle) with 100 revolutions/min in phosphate buffer of pH 7.5 to the extent of more than 80% after 30 min." Beckert's Figure 1 shows that far less than 80% of an alternative active ingredient will be released from uncoated pellets in a comparable test after 1 hour at a pH of 7.0. From that comparative evidence, persons having ordinary skill in the art reasonably would have expected that Applicant's polymeric or copolymeric binder with acidic groups significantly improved the solubility and release characteristics of budesonide. Beckert's Figure 1 shows a release of far less than 80% of an alternative active ingredient from uncoated pellets after 1 hour at a pH of 7.0. Applicant's claims require release of more than 80% of budesonide from the inner layer of its claimed pharmaceutical formulation at a pH of 7.5 after 30 minutes.

Applicant's Specification gives notice that budesonide is an active agent with comparatively low solubility (Spec., p. 2, ll. 33-35; p. 16, ll. 10-17). The active agent required in all of Applicant's current claims is budesonide and the extent of its release in an intestinal environment is more than 80% after 30 minutes. In support of Applicant's claims, Example 1 on pages 27-28 of the Specification shows that budesonide without binder has a very low release rate in water buffered to a pH of 7.5 after 1 hour. The release rate shown for

budesonide in Example 1 on pages 27-28 appears to be much less than that indicated in Figure 1 of Beckert '454 for what is suggested to be an active ingredient comparable in effect to budesonide. The Examiner apparently also failed to consider the significantly increased release rates for budesonide which Applicant reported in Examples 2-3 on pages 28-30 of the Specification. There budesonide is bound in Eudragit® L 30 D-55, a copolymer with acidic groups in accordance with Applicant's Claim 2 (Spec., p. 7, ll. 18-22). Thus, the evidence in the Specification confirms that the release rates for budesonide bound in a binder which is a polymer or copolymer with acidic groups as per Applicant's claimed pharmaceutical formulation is significantly improved over the release rates shown and/or suggested by Beckert '454 and are entirely unexpected in view of Beckert's teaching as a whole.

The Examiner ultimately concluded that the formulation Applicant claims would have been prima facie obvious to a person having ordinary skill in the art in view of Beckert's disclosure as a whole, whether or not Beckert '454 disclosed or reasonably suggested using a polymer or copolymer with acidic groups to bind budesonide in the core of its multilayer pharmaceutical product (OA, p. 6; AA, p. 2). The Examiner's conclusion is contrary to legal precedent. To establish the *prima facie* obviousness of the claimed subject matter, there must be some suggestion, incentive, or motivation to do what Applicant has done. That suggestion can be found either in the applied references or in the general knowledge of persons having ordinary skill in the art. *In re Jones*, 958

F.2d 347, 351 (Fed. Cir. 1992); *In re Fine*, 837 F.2d 1071, 1074 (Fed. Cir. 1988). However, where there is no reasonable instruction, no suggestion, no motivation, and no incentive in the prior art to make the chemical modifications necessary to arrive at Applicant's claimed pharmaceutical formulation, a prima facie case of obviousness has not been established. *See In re Grabiak*, 769 F.2d 729, 731-32 (Fed. Cir. 1985) ("[T]here must be adequate support in the prior art for the [prior art] ester/[claimed] thioester change in structure, in order to complete the PTO's *prima facie* case . . . ."); *In re Lalu*, 747 F.2d 703, 705 (Fed. Cir. 1984)("The prior art must provide one of ordinary skill in the art the motivation to make the proposed molecular modifications needed to arrive at the claimed compound."). In this case, the Examiner has not pointed to any teaching or suggestion, and has not identified any motivation, to use polymers or copolymers with acidic groups as a binder for budesonide at the core of Beckert's multilayer pharmaceutical product. Moreover, the comparative evidence of record surprisingly shows that Applicant's claimed formulation with an inner layer of budesonide bound in a polymeric or copolymeric binder with acidic groups is far superior in rate of releasing budesonide in an intestinal environment to otherwise identical formulations with an inner layer of budesonide either unbound or bound to a polymeric binder without acidic groups such as sucrose and Kollidon® 25. The collective evidence favoring patentability substantially outweighs the evidence to the contrary. Accordingly,

the Examiner's final rejection of Claim 1 and all claims dependent thereon should be REVERSED.

2. Rejection of Claim 3 under 35 U.S.C. § 103 in view of Beckert

Applicant feels constrained to separately argue the rejection of Applicant's Claim 3 under 35 U.S.C. § 103 in view of Beckert. The PTO has the initial burden of proof to establish the factual basis for its rejections under 35 U.S.C. 103. *In re Piasecki*, 745 F.2d 1468, 1472 (Fed. Cir. 1984). The Examiner has not explained why dependent Claim 3 wherein the polymeric binder which binds budesonide in the inner layer of the claimed pharmaceutical formulation is a vinylpyrrolidone/vinyl acetate would have been prima facie obvious in view of Beckert's disclosure of a Kollidon® 25 PVP binder. The Examiner has not established that previously presented dependent Claim 3 would have been prima facie obvious to a person having ordinary skill in the art in view of any other Beckert '454 teaching. As the collective evidence in the examples in Applicant's Specification and Beckert '454 shows, not all binders release the content of an active ingredient bound therein at the same rate in an intestinal environment. Beckert '454 provides persons having ordinary skill in the art with no more than an invitation to experiment with no instruction, guidance, or incentive to do what Applicant has done, no recognition of the problem, and no concern with improving the rate of release of budesonide in an intestinal environment or reasonable expectation of successfully doing so.

3. Rejection of Claim 4 under 35 U.S.C. § 103 in view of Beckert

We also separately argue the rejection of Applicant's Claim 4 under 35 U.S.C. § 103 in view of Beckert. Again, the PTO has the initial burden of proof to establish the factual basis for its rejections under 35 U.S.C. 103. *In re Piasecki*, 745 F.2d at 1472. The Examiner has not explained why dependent Claim 4 wherein the intermediate layer is a (meth)acrylate copolymer which comprises 40 to 100% by weight free-radical polymerized units of C_1- to C_4-alkyl esters of acrylic or methacrylic acid and no or up to 60% by weight (meth)acrylate monomers with an anionic group in the alkyl radical would have been prima facie obvious in view of Beckert's disclosure of an intermediate layer comprising a (meth)acrylate copolymer which comprises 85 to 98% by weight free-radical polymerized C_1- to C_4-alkyl esters of acrylic or methacrylic acid and 15 to 2% by weight (meth)acrylate monomers with a cationic quaternary ammonium group in the alkyl radical (Beckert '454, col. 4, l. 53, to col. 5, l. 41). Cationic quaternary ammonium groups are not anionic acidic groups. Beckert '454 does not teach or reasonably suggest that its inner layer, i.e., the intermediate layer of Applicant's claimed multilayer formulation, should or may be a polymer or copolymer with anionic acidic groups or a polymer or a (meth)acrylate copolymer free of quaternary ammonium groups. While Beckert's outer layer may indeed be a polymer or copolymer with acidic groups, Beckert '454 does not invite persons having ordinary skill in the art to make the outer layer the inner layer or vice versa, or arbitrarily pick and choose

components from an outer layer resistant to gastric juices and put them anywhere they please. Obviousness is not an open invitation to experiment.

The Examiner has not established that previously presented dependent Claim 4 would have been prima facie obvious to a person having ordinary skill in the art in view of Beckert's teaching. Prima facie obviousness requires some suggestion to do what the applicant has done with a reasonable expectation of success. *In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988). The Examiner's final rejection of Claim 4 should be reversed.

4. Rejection of Claim 11 under 35 U.S.C. § 103 in view of Beckert

The Examiner has not pointed to any teaching in Beckert or knowledge in the pertinent art which supports the rejection of Applicant's Claim 11 under 35 U.S.C. § 103 in view of Beckert. Again, the PTO has the initial burden of proof to establish the factual basis for its rejections under 35 U.S.C. 103. *In re Piasecki*, 745 F.2d at 1472. The Examiner has not explained why persons having ordinary skill in the art would employ two different kinds of the pharmaceutical formulations Beckert discloses in a multiparticulate pharmaceutical form with substantially uniform release of budesonide in the small intestine and in the large intestine, where one type of formulation releases the active ingredient predominantly in the pH range of the small intestine and the other type of formulation releases the active ingredient predominantly in the pH range of the large intestine. Beckert '454 does not recognize that the release of active ingredient may differ dependent on the environment in the small or

large intestine. Moreover, even if persons having ordinary skill in the pertinent art would have had that particular knowledge, nothing in Beckert '454 would have enabled persons having ordinary skill in the art to make and effectively use the multiparticulate pharmaceutical formulation of Applicant's Claim 11 with reasonable expectation of success. With no guidance whatsoever in Beckert '454, undue experimentation would have been required for a person skilled in the art to make and use the invention of Applicant's Claim 11. Accordingly, the final rejection of Applicant's Claim 11 should be reversed.

CONCLUSION

For the reasons stated herein:

1. The rejections of Claims 1, 2, 5-8, 10. and 12 under 35 U.S.C. § 103 as unpatentable over Beckert should be REVERSED.

2. The rejections of Claim 3 under 35 U.S.C. § 103 as unpatentable over Beckert should be REVERSED.

3. The rejections of Claim 4 under 35 U.S.C. § 103 as unpatentable over Beckert should be REVERSED.

11. The rejections of Claim 11 under 35 U.S.C. § 103 as unpatentable over Beckert should be REVERSED.

Respectfully submitted,

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CLAIMS APPENDIX

Claim 1 (Rejected): A pharmaceutical formulation comprising

a) an inner layer with the active ingredient budesonide bound in a binder

b) an intermediate layer with a polymeric coating agent which is soluble in intestinal juice or extends release,

c) an outer envelope which is resistant to gastric juice or an outer layer with a coating agent which is resistant to gastric juice

where the layers may comprise further pharmaceutically acceptable excipients,

wherein the binder is a polymer or copolymer with acidic groups, and the formulation of the inner layer without intermediate and outer layer releases the bound active ingredient in the release test according to USP XXIII monograph <711> "Dissolution" with apparatus 2 (paddle) with 100 revolutions/min in phosphate buffer of pH 7.5 to the extent of more than 80% after 30 min.

Claim 2 (Rejected): The pharmaceutical formulation as claimed in claim 1, wherein the polymeric binder is a (meth)acrylate copolymer which comprises 40 to 95% by weight free-radical polymerized units of C_1- to C_4-alkyl esters of acrylic or methacrylic acid and 5 to 60% by weight (meth)acrylate monomers with an anionic group in the alkyl radical.

Claim 3 (Rejected): The pharmaceutical formulation as claimed in claim 1, wherein the polymeric binder is a vinylpyrrolidone/vinyl acetate copolymer.

Claim 4 (Rejected): The pharmaceutical formulation as claimed in claim 1, wherein the intermediate layer is a (meth)acrylate copolymer which comprises 40 to 100% by weight free-radical polymerized units of C_1- to C_4-alkyl esters of acrylic or methacrylic acid and no or up to 60% by weight (meth)acrylate monomers with an anionic group in the alkyl radical.

Claim 5 (Rejected): The pharmaceutical formulation as claimed in claim 1, wherein the intermediate layer is a (meth)acrylate copolymer which comprises 85 to 98% by weight free-radical polymerized units of C1- to C4-alkyl esters of acrylic or methacrylic acid and 15 to 2% by weight (meth)acrylate monomers with a quaternary ammonium group in the alkyl radical.

Claim 6 (Rejected): The pharmaceutical formulation as claimed in claim 1, wherein the outer coating agent which is resistant to gastric juice is a (meth)acrylate copolymer which comprises 40 to 100% by weight free-radical polymerized units of C_1- to C_4-alkyl esters of acrylic or methacrylic acid and 5 up to 60% by weight (meth)acrylate monomers with an anionic group in the alkyl radical.

Claim 7 (Rejected): The pharmaceutical formulation as claimed in claim 1, wherein the outer envelope which is resistant to gastric juice is a capsule.

Claim 8 (Rejected): The pharmaceutical formulation as claimed in claim 7, wherein the capsule consists essentially of gelatin or of hydroxypropycellulose.

Claim 9 (Cancelled).

Claim 10 (Rejected): The pharmaceutical formulation as claimed in claim 6, wherein the pharmaceutical formulation comprises the active ingredient in the form of pellets or granules.

Claim 11 (Rejected): The pharmaceutical formulation as claimed in claim 1, wherein the pharmaceutical formulation is a multiparticulate pharmaceutical form with substantially uniform release of budesonide in the small intestine and in the large intestine, which comprises at least two different types of pellets, one type of pellet releasing the active ingredient predominantly in the pH range of the small intestine and the other predominantly in the pH range of the large intestine.

Claim 12 (Rejected): The pharmaceutical formulation as claimed in claim 11, wherein the pellets are enclosed in a capsule comprising (meth)acrylate copolymer which comprises 40 to 100% by weight free-radical polymerized units of C_1- to C_4-alkyl esters of acrylic or methacrylic acid and 5 up to 60% by weight (meth)acrylate monomers with an anionic group in the alkyl radical.

Claims 13-16 (Cancelled).

Claim 17 (Withdrawn): A pharmaceutical formulation comprising

a) an inner layer with the active ingredient budesonide bound in a binder which is a (meth)acrylate copolymer which comprises 40 to 95% by weight free-radical polymerized units of C_1- to C_4-alkyl esters of acrylic or methacrylic acid and 5 to 60% by weight (meth)acrylate monomers with an anionic group in the alkyl radical

b) an intermediate layer with a polymeric coating agent which is a (meth)acrylate copolymer which comprises 85 to 98% by weight free-radical polymerized units of C1- to C4-alkyl esters of acrylic or methacrylic acid and 15 to 2% by weight (meth)acrylate monomers with a quaternary ammonium group in the alkyl radical and that is soluble in intestinal juice or extends release,

c) an outer envelope which is a (meth)acrylate copolymer which comprises 40 to 100% by weight free-radical polymerized units of C_1- to C_4-alkyl esters of acrylic or methacrylic acid and 5 up to 60% by weight (meth)acrylate monomers with an anionic group in the alkyl radical and that is resistant to gastric juice or an outer layer with a coating agent which is resistant to gastric juice

where the layers may comprise further pharmaceutically acceptable excipients,

wherein the binder is a polymer or copolymer with acidic groups, and the formulation of the inner layer without intermediate and outer layer releases the bound active ingredient in the release test according to USP XXIII monograph <711> "Dissolution" with apparatus 2 (paddle) with 100 revolutions/min in phosphate buffer of pH 7.5 to the extent of more than 80% after 30 min.

CLAIM SUPPORT AND DRAWING ANALYSIS SECTION

There are no drawings associated with the Application on appeal.

Multilayer pharmaceutical formulations of Claim 1 which release 80% of its active budesonide content after 30 minutes in an intestinal environment is supported in the Specification at page 1, lines 6-7, and page 3, line 22, to page 4, line 12. The pharmaceutical formulation of Claim 1 comprising: (a) an inner layer comprising budesonide as the active ingredient bound in a polymeric or copolymeric binder with acidic groups, (b) an intermediate layer including a

polymeric material which is soluble in the intestinal juice or extends release, and (c) an outer layer including a polymer resistant to gastric juice or an envelope resistant to gastric juice is supported in the Specification at page 4, line 16, to page 5, line 5.

The invention of separately argued dependent Claim 3 wherein the inner layer (a) comprises budesonide bound in vinylpyrrolidone/ vinyl acetate copolymer is supported in the Specification at page 9, lines 27-34). The invention of separately argued dependent Claim 4 wherein intermediate layer (b) is a (meth)acrylate copolymer which comprises 40 to 100% by weight free-radical polymerized units of C_1- to C_4-alkyl esters of acrylic or methacrylic acid and no or up to 60% by weight (meth)acrylate monomers with an anionic group in the alkyl radical is supported in the Specification at page 10, lines 21-26. The invention of separately argued dependent Claim 11 wherein the pharmaceutical formulation is a multiparticulate form which comprises different types of pellets, where one type uniformly releases budesonide in the small intestines and the other type uniformly releases budesonide in the large intestines is supported in the Specification at page 20, lines 6-34.

MEANS OR STEP PLUS FUNCTION APPENDIX

There are no claims with means or step plus function language on appeal.

EVIDENCE APPENDIX

Affidavits and Declarations

No secondary evidence in the form of an affidavit or declaration is relied upon in support of the findings and arguments in this appeal.

Other Evidence (attached)

"Soluble Kollidon® grades," BASF Technical Information brochure dated January 2004, BASF Chemical Co., pages 1-14.

RELATED PROCEEDINGS APPENDIX

Appellant/Applicant, Appellant/Applicant's legal representative[s], and Appellant/Applicant's assignee[s], are aware of no appeals, interferences, or judicial proceedings that are related to, directly affect or would be directly affected by, or have a bearing on the decision of the Board of Patent Appeals and Interferences in this appeal.

Technical Information

January 2004
Supersedes issue of February 2001

Register 2

Soluble Kollidon® grades

® = Registered trademark of
BASF Aktiengesellschaft

Soluble polyvinylpyrrolidone (Povidone Ph.Eur, USP, JP) for the pharmaceutical industry

Fine Chemicals

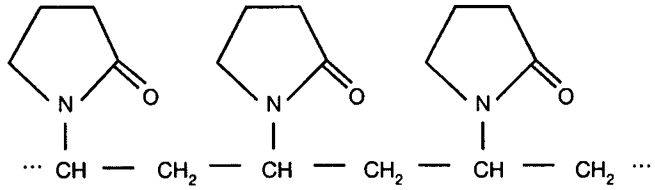
BASF

Contents

1 Introduction

1.1 General

The foundations of modern acetylene chemistry were laid by Reppe at BASF. One of the many products to emerge from this work was soluble polyvinylpyrrolidone, which is obtained by radical polymerization of N-vinylpyrrolidone



Monomer unit: 111.14

Because of its solubility in water and in many organic solvents, its high binding power and ability to form complexes, soluble polyvinylpyrrolidone occupies a special position among the synthetic colloids.

Separate Technical Data Sheets are available for the insoluble Kollidon grades (crospovidone) and for Kollidon VA 64, a copolymer of N-vinylpyrrolidone and vinyl acetate (copovidone).

More information on Kollidon than can be provided in this brochure may be found in the book, "Kollidon, Polyvinylpyrrolidone for the Pharmaceutical Industry" 7th edition 2003, also available as CD-ROM.

1.2 Synonyms

Soluble polyvinylpyrrolidone is also known as povidon(e), povidonum, polyvidone, poly(1-vinyl-2-pyrrolidone) and PVP.

1.3 Range

As the requirements differ considerably in the various fields of application, it has been found necessary to create two product lines: the Kollidon grades for pharmaceutical products and the Luviskol® grades for cosmetics and technical applications.

The Kollidon range consists of the following products:

	PBG-Number
Kollidon 12 PF	10 011 265
Kollidon 17 PF	10 010 750
Kollidon 25	10 000 996
Kollidon 30	10 066 831
Kollidon 90 F	10 096 088

2 Specifications and stability

2.1 Specifications

All the soluble grades of Kollidon are of pharmaceutical purity and meet the following specifications:

Table 1 Specifications of the soluble grades of Kollidon

	Kollidon 12 PF	Kollidon 17 PF	Kollidon 25	Kollidon 30	Kollidon 90 F
Colour (10% in water)	lighter than B6/BY6/R6	lighter than B6/BY6/R6	lighter than B6/BY6/R6	lighter than B6/BY6/R6	lighter than B6/BY6/R6
Clarity (10% in water)	clear	clear	clear	clear	clear
K-value	10.2–13.8	15.3–18.0	22.5–27.0	27.0–32.4	81.0–96.3
Nitrogen content	11.5–12.8	12.0–12.8	12.0–12.8	12.0–12.8	12.0–12.8
Water (Karl Fischer), %	≤ 5.0	≤ 5.0	≤ 5.0	≤ 5.0	≤ 5.0
pH value (5 % in water)	3.0–5.0	3.0–5.0	3.0–5.0	3.0–5.0	4.0–7.0
Vinylpyrrolidone (HPLC), ppm	≤ 5	≤ 5	≤ 10	≤ 10	≤ 10
Sulfated ash, %	≤ 0.1	≤ 0.1	≤ 0.1	≤ 0.1	≤ 0.1
Aldehyde, ppm	≤ 500	≤ 500	≤ 500	≤ 500	≤ 500
Heavy metals, ppm	≤ 10	≤ 10	≤ 10	≤ 10	≤ 10
Hydrazine, ppm	≤ 1	≤ 1	≤ 1	≤ 1	≤ 1
Peroxides (as H_2O_2), ppm	≤ 400	≤ 400	≤ 400	≤ 400	≤ 400
Microbial status (see Table 3)	passes test	passes test	passes test	passes test	passes test
Endotoxins (Ph.Eur.) (6% solution)	≤ 6 I.U./ml (≤ 0.1 I.U./mg)	≤ 6 I.U./ml (≤ 0.1 I.U./mg)	not tested	not tested	not tested
Residual solvents (Ph. Eur. 5.4)	≤ 0.5% 2-propanol	≤ 0.5% 2-propanol	≤ 0.5% formic acid	≤ 0.5% formic acid	≤ 0.5% formic acid
2-pyrrolidone	≤ 1.0%	≤ 1.0%	≤ 3.0%	≤ 3.0%	≤ 1.0%

All the physical and chemical properties are determined by the methods in the European Pharmacopoeia or the USP.

2.2 Pharmacopoeias

All the Kollidon grades meet the requirements of the current harmonized monographs for povidone in the following pharmacopoeias:

Table 2 Soluble Kollidon in the Pharmacopoeias

Product name	Ph. Eur.	USP/NF	JP/JPE
Kollidon 12 PF	+	+	n. a.
Kollidon 17 PF	+	+	+
Kollidon 25	+	+	+
Kollidon 30	+	+	+
Kollidon 90 F	+	+	+

n. a. = not available

2.3 Microbial status, endotoxins

The microbial status is determined by Ph. Eur. 4 methods 2.6.12 and 2.6.13. The limits given in the European Pharmacopoeia (Table 3) apply to all the soluble Kollidon grades.

Table 3 Microbial purity requirements (Ph. Eur. 4, 5.1.4, Categories 2 + 3A)

- Max. 10^2 aerobic bacteria and fungi/g
- No Escherichia coli/g
- Max. 10 Enterobacteriaceae and other gram-negative bacteria/g
- No Pseudomonas aeruginosa/g
- No Staphylococcus aureus/g

Kollidon 12 PF and Kollidon 17 PF are tested for bacterial endotoxins by Method 2.6.14 in the 4th edition of the European Pharmacopoeia. A 6% solution of Kollidon in isotonic sodium chloride solution is tested.

2.4 Residual solvents

The Kollidon grades fulfill the requirements of the ICH guidelines (Class 3, Ph. Eur. 5.4)

2.5 Stability and storage

The soluble Kollidon grades retain the properties given in the specifications over a period of more than three years, if they are stored in the unopened original containers at room temperature (20–25 °C). Kollidon 90 F is an exception in that, under these conditions, its stability can be guaranteed, as its K value gradually decreases.

If Kollidon 90 F is kept refrigerated, its K value decreases more slowly.

Kollidon must be stored tightly closed and protected from light at max. 25 °C.

2.6 Packaging

Kollidon 12 PF and Kollidon 17 PF: 50-kg PE drum with PE inliner.

Kollidon 90 F: 25-kg carton with welded PE/aluminium inliner.

Kollidon 25 and Kollidon 30:
until 2001: 50-kg drum with PE inliner
from August 2001: 25-kg carton with welded PE/aluminium inliner.

3 Physical and chemical properties

3.1 Description

All grades of Kollidon are supplied in the form of an almost white free-flowing powder. They have a slight characteristic odour and are practically tasteless.

3.2 Solubility

The solubility of Kollidon varies considerably from one solvent to another. In Table 4 below, "soluble" signifies that a solution of at least 10% can be prepared, and "insoluble" signifies that the solubility is less than 1%.

Table 4 Solubility of Kollidon

Soluble in:	
chloroform	n-butanol
cyclohexanol	n-propanol
ethanol abs.	polyethylene glycol 400
glycerine	(= Lutrol® E 400)
isopropanol	propylene glycol
methanol	triethanolamine
methylene chloride	water
Insoluble in:	
cyclohexane	pentane
diethyl ether	carbon tetrachloride
ethyl acetate	toluene
liquid paraffin	xylene

3.3 Hygroscopicity

The hygroscopic nature of Kollidon is important in many applications. There is hardly any difference between the individual grades so that the same curve applies to all (Fig. 1).

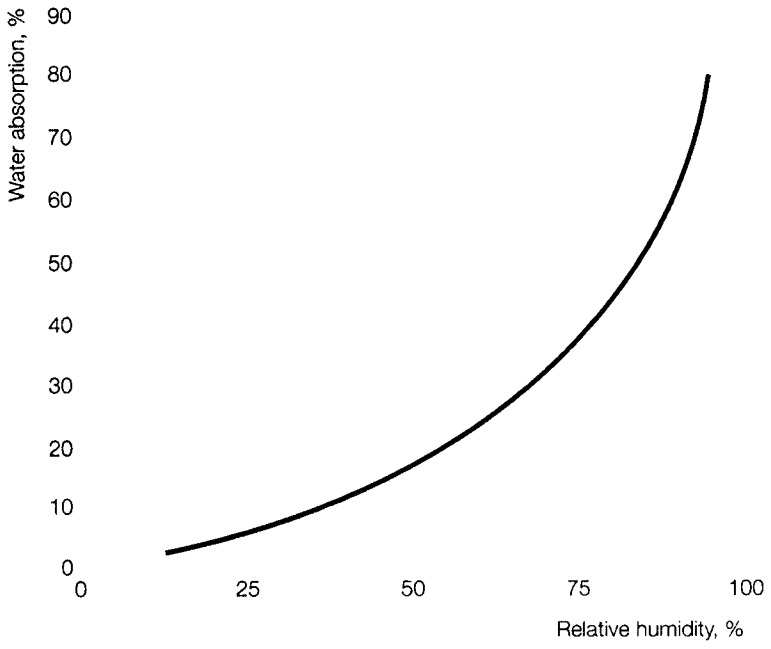


Fig. 1 Hygroscopicity of soluble Kollidon

3.4 Viscosity

Fig. 2 shows the relationship between the viscosity of aqueous solutions of the different grades of Kollidon and their concentration.

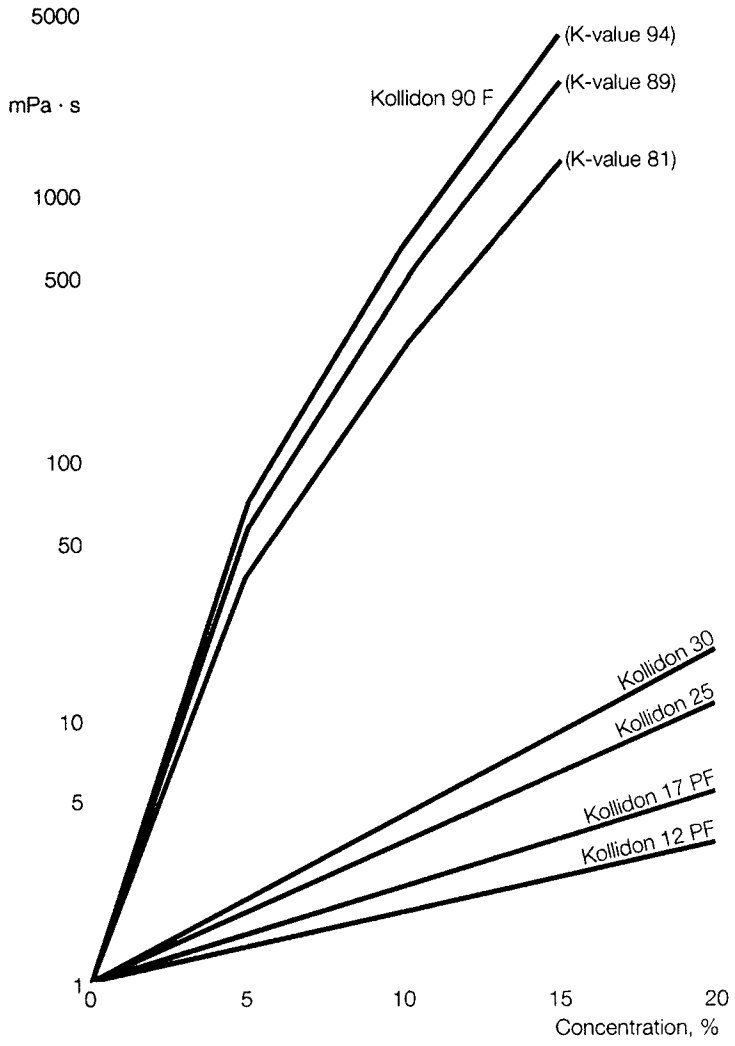


Fig. 2 Viscosity of Kollidon solutions (Ubbelohde viscometer, 25 °C)

3.5 Particle-size distribution

In the pharmaceutical technology of solid dosage forms, particularly in the direct compression of tablets, the particle-size distribution of the solid ingredients used is a factor of some significance.

The following table gives some typical particle-size distribution values (determined in an air-jet sieve; 5 min, 20 mbar):

Table 5 Particle-size distribution, %

	< 50	> 250
Kollidon 25/30	approx. 10	max. 5
Kollidon 90 F	max. 10	max. 20

3.6 Bulk density

The bulk density of Kollidon is determined according to Ph. Eur. 4, Section 2.9.16.

Table 6 Bulk density of the Kollidon grades

Kollidon 12 PF	400–600 g/l
Kollidon 17 PF	400–600 g/l
Kollidon 25/30	400–600 g/l
Kollidon 90 F	400–550 g/l

3.7 Stability in solution, sterilization

Aqueous solutions of povidone have no buffering action. If left to stand, and particularly if heated, they take on a slight yellowish colour. The yellowing can be diminished by adding a reducing agent, e. g. sodium metabisulfite or cystein. Local legislation on the use of sodium metabisulfite in parenterals must be observed.

For sterilization purposes, 0.01–0.1% sodium metabisulfite or 0.05–0.1% cystein, as a proportion of the Kollidon, is added to the solution which is then heated in the absence of air.

3.8 Complexation, chemical interactions

Povidone can form fairly stable association compounds or complexes with a number of active substances. The best known example is PVP-iodine which is the subject of a separate leaflet.

The ability of Kollidon to form a water-soluble complex with insoluble active substances can be used in pharmaceuticals to improve the release rate and solubility of drugs (see Sections 4.3 and 4.4).

There are a few substances such as the polyphenols that form stronger complexes that can precipitate in neutral or acidic media. This effect can be used in the removal of polyphenols and anthocyanogens from solutions or beverages. However, insoluble polyvinylpyrrolidone (Kollidon CL) is most suitable for this purpose.

It must be noted that if povidone is combined with strongly alkaline substances such as lithium carbonate or sodium hydroxide it can crosslink and become insoluble, particularly at elevated temperatures. In extreme cases, this can increase the viscosity of liquid presentation forms and delay bioavailability in solid presentation forms.

3.9 Molecular weight

With polymers generally, the average molecular weight can be expressed in three forms: weight, number and viscosity average.

The molecular weight of povidone is usually expressed as the K-value, from which it is possible to calculate the viscosity average molecular weight (M_v).

However, the weight average molecular weight (M_w) is found more frequently in the literature. It is determined by methods such as light scattering that measure the weight of the molecules.

The following M_w values were determined for different grades of Kollidon in recent measurements.

Kollidon 12 PF	2000	–	3000
Kollidon 17 PF	7000	–	11000
Kollidon 25	28000	–	34000
Kollidon 30	44000	–	54000
Kollidon 90 F	1000000	–	1500000

Earlier measurements of M_w that were not quite so accurate gave values of 40,000 for Kollidon 30 and 700,000 for Kollidon 90, for example.

3.10 Safety Data Sheets

Safety Data Sheets for the individual grades of Kollidon are available on request.

4 Applications

4.1 General

The main applications of the soluble Kollidon grades are summarised in Table 7.

Table 7: Main applications of the soluble Kollidon grades

Binder	Tablets, capsules, granules
Bioavailability enhancement	Tablets, capsules, granules, pellets, suppositories, transdermal systems
Film formation	Opthalmic solutions, tablets, medical plastics
Solubilization	Oral, parenteral and topical solutions
Taste masking	Oral solutions
Lyophilising agent	Injection preparations, oral lyophilisates
Stabilisation of suspensions	Oral and parenteral suspensions, instant beverage powders and granules
Hydrophylization	Medical plastics, retard preparations, suspensions
Adhesives	Transdermal systems, adhesive gels
Drug stabilisation	Enzymes in diagnostics
Toxicity reduction	Injection preparations

The adhesive, film-forming, dispersing and thickening properties of the soluble Kollidon grades are used in tablet production, sugar coating, film coating and in the preparation of other dosage forms. The improvement in the solubility of active ingredients brought about by complexation or association, and the thickening effect find use mainly in the manufacture of liquid presentation forms.

The grade of Kollidon that is selected depends mainly on its molecular weight, as this dictates the viscosity, binding effect, the complexation capacity and how readily it is eliminated from the body.

A detailed description of the applications is to be found in the book, "Kollidon, polyvinylpyrrolidone for the Pharmaceutical Industry" (BASF, MEFM09015e, 2003 edition).

4.2 Tablet binders

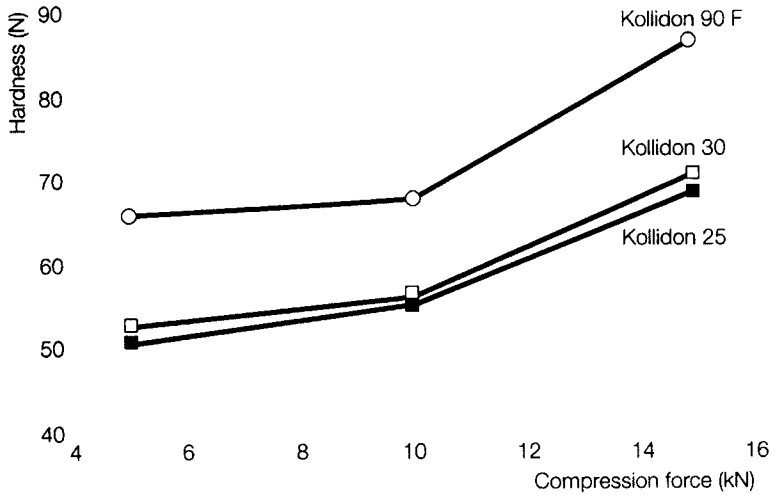
Kollidon 25, 30 and 90 F

Kollidon 25, 30 and 90 F give hard, free-flowing granules for tablet making with a low proportion of fines and high binding strength. For Kollidon 25 and 30, the quantity required lies between 2% and 5% of the tablet weight. For Kollidon 90 F, less than 2% is generally required, because of its great binding capacity. The high viscosity of binder solutions made with Kollidon 90 F sometimes requires certain precautions to ensure that the granules are evenly wetted. Granulators or spraying machines that have a strong mixing action are helpful.

The addition of polyethylene glycol 400 (Lutrol E 400) as a plasticizer or the replacement of the povidone with Kollidon VA 64 is often helpful if the granules are too brittle.

Kollidon 25, 30 and 90 F are also suitable for the direct compression of tablets without granulation (prior to 1993, Kollidon 90 was unsuitable for this purpose because of its particle size). This technique requires a certain relative humidity, as the powder mixture must have a certain moisture content to bind properly. If Kollidon is used in addition to microcrystalline cellulose, it not only makes the tablets harder but also gives them stronger edges. For best results in direct compression, all the excipients should have a certain moisture content. This applies to starch, microcrystalline cellulose and lactose monohydrate as fillers.

It can be seen from Fig. 3 that there is hardly any difference in the hardness of lactose placebo tablets made with Kollidon 25 and Kollidon 30. However, the same quantity (3 % of the tablet weight) of Kollidon 90 F almost doubles the hardness, compared with Kollidon 25.



Kollidon 30 can be prepared relatively quickly, and sprayed easily, to quickly give hard dust-free uniform granules. If the spray includes pigments, Kollidon improves their distribution.

A typical formulation for wet granulation with Kollidon 30 is given below in Table 8 for alpha-methyldopa tablets. The formulation was tried out on a laboratory scale.

Table 8 Alpha-methyldopa tablets and cores (275 mg)

I	Alpha-methyldopa	275 g
	Lactose monohydrate	55 g
II	Kollidon 30	15 g
	Isopropanol	80 ml
III	Kollidon CL	8 g
	Magnesium stearate	2 g

Granulate mixture I with solution II, dry, sieve, mix with the ingredients in III and compress into tablets on a rotary tablet press with medium force (approx. 15 kN).

The tablets produced in the laboratory had the following properties:

Weight (measured)	361 mg
Diameter:	12 mm
Hardness:	118 N
Disintegration time (gastric juice):	5 min
Friability:	0 %
Dissolution acc. to USP in 0.1 N hydrochloric acid:	15 min: 77% 30 min: 98%

4.3 Solubilization

Some examples are given as in Table 9 of typical drugs that can be solubilized with soluble Kollidon.

Table 9 Some of the active ingredients that can be solubilized with soluble Kollidon

Acetaminophen (paracetamol)	Oxytetracycline
Allopurinol	Reserpine
Amoxicillin	Rifampicin
Chloramphenicol	Sulfadimethoxine
Clonazepam	Sulfamethazine
Coumarin	Sulfamoxole
Diclofenac-Na	Sulfathiazole
Doxycycline	Tranilast
Furaltadone	Trimethoprim
Hydroflumethiazide Nitrofural	Tyrothricin

Kollidon 12 PF, 17 PF

The low-molecular grades, Kollidon 12 PF and Kollidon 17 PF are intended for use as solubilizing agents, dispersants and crystallization inhibitors particularly for injectables.

These properties are of particular interest for antibiotics in solution or lyophylisate form.

Kollidon 25, 30

In the same way as Kollidon 12 PF and Kollidon 17 PF are used in injectables, Kollidon 25 and 30 can be used in preparations for oral or external application as solubilizers for the same active ingredients. One typical example is the formulation for a paracetamol syrup, in which Kollidon 25 increases the solubility of the active substance and also reduces its bitter taste.

4.4 Coprecipitation, comilling

Kollidon 25, 30

The dissolution rate and therefore the absorption rate of drugs that do not dissolve readily in water can be greatly improved by comilling or coprecipitation with Kollidon 25 or Kollidon 30, as the complex formed is, in effect, a solid solution of the drug in the Kollidon. This requires an excess of Kollidon to maintain the (partially) amorphous form of the active substance. Suitable processes include mixing, comilling or melt extrusion of the Kollidon-drug mixture, or coprecipitation, granulation onto a carrier, or spray-drying a solution containing the drug and Kollidon.

The literature contains hundreds of publications on this application. The most frequently tested active substance mentioned is probably nifedipine.

4.5 Suspension stabilizer

Kollidon 25, 30, 90 F

Kollidon 25, 30 and 90 F can be used to stabilize oral and topical suspensions with a wide range of active ingredients, e. g. acyclovir, ibuprofen, magaldrate, nystatin, phenytoin, trimethoprim, sulfonamides and antibiotics, as well as sugar-coating suspensions. Combinations of Kollidon 90 F with Kollidon CL-M have often given very good results.

Kollidon 12 PF, Kollidon 17 PF

The low-molecular endotoxin-free grades of Kollidon can be used to stabilize parenteral suspensions. This applies particularly to antibiotic

4.6 Thickener

Kollidon 90 F

Because of its good solubility in water and alcohol, Kollidon 90 F can be used as a thickener for aqueous-alcoholic solutions for oral application (viscosity curve, see Section 3.4).

4.7 Use in ophthalmic preparations

Kollidon 17 PF, 25, 30, 90 F

Soluble Kollidon can also be used in eye preparations, because of its solubilizing, film-forming and thickening properties, for instance to ensure that the preparation remains in the eye for a certain time, to lubricate the eye, or to solubilize an active ingredient. This application requires between 2% and 10% Kollidon. It is added to some eye drops e. g. with pilocarpine, to prolong the therapeutic effect. The bioavailability of many active substances in ophthalmic preparations can also be improved or controlled by adding Kollidon.

Kollidon is also used in contact-lens cleaning fluids.

4.8 Sugar coating

Kollidon 25, 30

The good film-forming properties, great adhesive strength and very good dispersing action of Kollidon are very useful in both traditional and automatic sugar-coating processes. Kollidon 25 and 30 can be added to sugar-coating suspensions to prevent crazing of the sugar coating, and it also ensures that any pigments in the coating are evenly distributed and that the suspension remains stable. The sugar coating often develops crazing if the tablets are dried very quickly, resulting in a moisture gradient between the outside and the inside of the tablet, which can also happen if the suspension contains large quantities of pigment. Kollidon prevents the pigment particles from aggregating again and promotes the homogeneity of the sugar layer. Kollidon can also be used to prevent the migration of soluble dyes.

4.9 Film coatings

Kollidon 25 and Kollidon 30 are also very useful in film coating. They are used as film-forming agents, adhesion promoters and pigment dispersers; they also improve the solubility of the coating in water.

However, it must be noted that soluble Kollidon can never be used as the sole film-forming agent as it is very hygroscopic and the coatings it gives are too tacky.

Kollidon can be combined with all the usual film-forming agents such as cellulose derivatives or methacrylates. Alcoholic pigment suspensions can be prepared with a mixture of shellac and soluble Kollidon, and these give homogeneous coatings particularly in modern spray-coating and fluidized-bed machines. The addition of Kollidon 25 or Kollidon 30 improves the rate of disintegration in aqueous solution, as the film-forming agents usually used have poor solubility in water. In most cases, it is recommended to strongly dilute the suspension for spraying.

10% solutions of Kollidon 25 or Kollidon 30 in ethanol or isopropanol can be used for subcoating moisture-sensitive tablet cores.

4.10 Various applications

Apart from the applications described above, the soluble grades of Kollidon can be used for the following purposes:

- adhesives in adhesive gels, e. g. for dentures
- stabilization of nitroglycerin in transdermal systems
- in controlled release preparations and transdermal systems to regulate the release of active substances
- hydrophilization and pore formation in plastics for medical applications, e. g. "hollow fibres"
- reduction of the toxicity of certain active substances
- cryoprotection, lyophilisation
- enzyme stabilization, e. g. in diagnostics
- vitamin stabilization

4.11 Food products

In 1995, soluble polyvinylpyrrolidone (povidone) was assigned Europe number E 1201 for use in dietetic tablets, e. g. vitamin and dietary fibre tablets, and in sweeteners.

5 Toxicological data

Soluble polyvinylpyrrolidone has been used for decades in all kinds of pharmaceutical preparations, and there are many publications on its good tolerance. In 1987, its ADI value was set at 0–50 mg/kg body weight by the World Health Organization (WHO).

From this literature and the toxicity studies listed below, which were conducted with different grades of Kollidon, there emerges the following profile of action:

The tolerance of soluble Kollidon after oral absorption is very good on the acute time scale and after long-term administration. It is neither teratogenic, mutagenic nor carcinogenic.

It has good skin and mucous membrane tolerance.

It also shows very good tolerance after parenteral administration. The low-molecular grades are quickly eliminated from the system.

The following toxicological and biochemical studies have been carried out with the individual soluble grades of Kollidon.

Kollidon 12 PF:

Acute toxicity, mouse i. v.: LD_{50} > 11 g/kg
4-week toxicity, rat i. v.
Prenatal toxicity, rabbit i. v.
Excretion of C^{14}-labelled Kollidon 12 by female rats after intravenous administration
Renal elimination of C^{14}-labelled Kollidon 12 after intravenous administration

Kollidon 17 PF:

Acute toxicity, mouse i. v.: LD_{50} > 15 g/kg
Acute toxicity, rat oral: LD_{50} > 10 g/kg
Excretion of C^{14}-labelled Kollidon 17 by female rats after intravenous administration
Renal elimination of C^{14}-labelled Kollidon 17 after intravenous administration
Mucous membrane tolerance in rabbit's eye

Kollidon 25:

Acute toxicity, mouse i. v.: LD_{50} > 15 g/kg
Acute toxicity, rat oral: LD_{50} > 10 g/kg
2-year toxicity, rat oral
Prenatal toxicity, rat oral
Mucous membrane tolerance in rabbit's eye

Kollidon 30

Acute toxicity, mouse i. v.: LD_{50} > 15 g/kg
Acute toxicity, rat oral: LD_{50} > 10 g/kg
Test for mutagenic effect of single intraperitoneal application in male mice
Mucous membrane tolerance in rabbit's eye
Cytogenetic studies in Chinese hamsters after two intraperitoneal applications

Kollidon 90

Acute toxicity, rat oral: LD_{50} > 8.25 g/kg
4-week toxicity, rat oral
4-week toxicity, dog oral
Prenatal toxicity, rat oral
2-year toxicity, rat oral

We will be glad to provide you with abridged reports of all tests carried out by our toxicology department or copies of the original reports. They will be available to you after signing a confidentiality agreement.

Note

The information submitted in this publication is based on our current knowledge and experience. In view of the many factors that may affect processing and application, these data do not relieve processors of the responsibility of carrying out their own tests and experiments; neither do they imply any legally binding assurance of certain properties or of suitability for a specific purpose. It is the responsibility of those to whom we supply our products to ensure that any proprietary rights and existing laws and legislation are observed.

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